

Mechanism for the Reaction between Cyanide and Nickel(II) Triglycine

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The reaction of cyanide ion with nickel triglycine, NiH_2GGG^- (where GGG^- is the triglycinate ion and two protons are ionized from the peptide nitrogens) proceeds through a two-path mechanism. Both paths involve the formation of mixed complexes. The presence of cyanide in the mixed complex $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$ increases the kinetic stability of the imide groups. This increase in stability is great enough to eliminate any contribution from general acid catalysis. Through the formation of a second mixed complex, $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$, cyanide is capable of labilizing the trans imide groups which increases the reaction rate. Even though this increase is significant, it is small compared to the kinetic stability gained when the first complex forms.

Introduction

Nickel(II) forms a yellow square-planar complex with triglycine (NiH_2GGG^-) in which the peptide hydrogens are ionized and the nitrogens are coordinated.¹⁻³ When this complex reacts with aminocarboxylate ligands such as EDTA the blue Ni-EDTA complex results. EDTA is a very poor nucleophile in this reaction and except at high pH reacts through a general acid catalyzed, proton transfer limited mechanism.⁴ The EDTA acts as a scavenger after one proton has been added to a peptide nitrogen. The similar copper triglycine complex (CuH_2GGG^-) also exhibits this type of reactivity toward EDTA.⁵⁻⁷

When NiH_2GGG^- and CuH_2GGG^- react with straight-chain polyamine ligands such as triethylenetetramine, a non proton transfer limited mechanism is observed.^{8,9} In this case direct replacement of the triglycine is observed; however, the reactions are sensitive to steric interactions.

In the present work, the kinetics of the reaction of cyanide with NiH_2GGG^- are studied. The reaction proceeds stepwise through the formation of mixed complexes with the ultimate formation of $\text{Ni}(\text{CN})_4^{2-}$ and liberation of triglycine. The presence of cyanide in the mixed complexes has a great effect upon the lability of the imide groups. When one cyanide adds to NiH_2GGG^- , replacing the carboxylate donor, the resultant kinetic stabilization is large enough to reduce the proton-transfer contribution from water by at least a factor of 1000. When a second cyanide adds, forming $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$, cyanide is capable of labilizing the trans imide groups and thus increasing the rate of the substitution reaction.¹⁰

Experimental Section

Nickel(II) perchlorate stock solution was prepared from twice recrystallized $\text{Ni}(\text{ClO}_4)_2$ and standardized by EDTA titration.¹¹ Sodium cyanide solutions (0.1 M) were standardized by the argenti-

metric method.¹² Twice recrystallized sodium perchlorate was used for ionic strength control. Boric acid-sodium borate was used for hydrogen ion control in some of the kinetic runs. Hydrogen ion concentrations were calculated using the relationships $-\log [\text{H}^+] = \text{pH} - 0.10$, where the pH was standardized with NBS buffers.

Solutions of triglycine were freshly prepared from the chromatographically pure solid (Mann Research Laboratories, New York, N. Y.). The NiH_2GGG^- solutions were prepared by the addition of NaOH to solutions containing 100% excess triglycine. The excess triglycine prevents the formation of $\text{Ni}(\text{OH})_2$ precipitate.

A $\text{p}K_a$ value of 9.0 was used for HCN which was calculated from a value of 9.14¹³ in 0.10 M (NaNO_3) and at 20° with correction to 25.0° using $\Delta H = 10.3$ kcal/mol.¹⁴ The first and second $\text{p}K_a$ values of nickel triglycine are 8.8 and 7.7, respectively.⁴

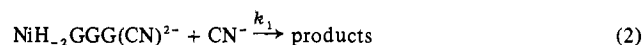
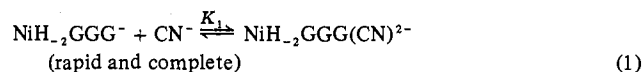
The rates of formation of $\text{Ni}(\text{CN})_4^{2-}$ were measured spectrophotometrically at 267 nm ($\epsilon = 1.16 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) and 285 nm ($\epsilon = 4.63 \times 10^3 \text{ M}^{-1} \text{ cm}^{-1}$). A typical reaction involved the preparation of a solution 10^{-5} M in nickel triglycine, 0.10 M in NaClO_4 , and of desired pH. A small volume of standard NaCN was added by syringe to the nickel complex solution. A Cary Model 14 spectrophotometer was used to record the absorbance values. The forward reactions were run in the presence of excess cyanide and all gave pseudo-first-order rate plots, $\ln(A_\infty - A_t)$ vs. time. A temperature of 25.0° was maintained for all reactions. The reported rate constants are an average of at least three kinetic runs.

Evidence of the mixed complex $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$ was obtained from the visible spectra of a series of solutions which had a nickel triglycine concentration of 2.88×10^{-4} M and a cyanide concentration ranging from 0.00 to 2.40×10^{-4} M. The absorption maximum shifts from 430 nm to shorter wavelengths as the $[\text{CN}^-]$ increases and an isosbestic point is observed at 406 nm. The complex exhibits an absorption maximum at 410 nm with a molar absorptivity of $1.74 \text{ M}^{-1} \text{ cm}^{-1}$. This complex shows no evidence of cyanide dissociation at pH values as low as 7 and thus indicates that the stability constant must be greater than 10^7 .

Results

The reaction of cyanide ion with NiH_2GGG^- does not form any $\text{Ni}(\text{CN})_4^{2-}$ until the ratio of CN^- to NiH_2GGG^- exceeds 1. This dependence results from the rapid and complete formation of the mixed complex $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$, eq 1.

First-order rate plots are observed when the cyanide concentration is much greater than the nickel triglycine concentration. The order with respect to cyanide is greater than 1 and increases as the cyanide concentration increases. The proposed reaction sequence is shown in eq 1-4. A rate equa-



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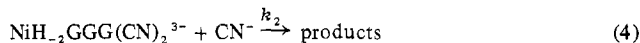
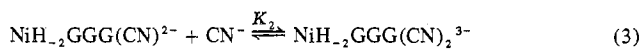
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tion consistent with the data for the formation of $\text{Ni}(\text{CN})_4^{2-}$ at pH 11 is shown in eq 5. As the cyanide concentration in-

$$\frac{d[\text{Ni}(\text{CN})_4^{2-}]}{dt} = (k_1 [\text{CN}]_T + K_2 k_2 [\text{CN}]_T^2) \times \frac{[\text{NiH}_2\text{GGG}]_T}{(1 + K_2 [\text{CN}]_T)} \quad (5)$$

creases, the second term in eq 5 contributes more to the rate and thus an increase in cyanide order. If cyanide concentration is less than about $10^{-3} M$, $K_2 [\text{CN}]_T$ is small compared to 1 and the observed rate constant under pseudo-first-order conditions is eq 6. A plot of $k_{\text{obsd}}/[\text{CN}]_T$ vs.

$$k_{\text{obsd}} = k_1 [\text{CN}]_T + K_2 k_2 [\text{CN}]_T^2 \quad (6)$$

$[\text{CN}]_T$ is shown in Figure 1. The intercept is k_1 ($k_1 = 5.9 M^{-1} \text{sec}^{-1}$) and the slope is $K_2 k_2$ ($K_2 k_2 = 1.3 \times 10^3 M^{-2} \text{sec}^{-1}$). At higher concentrations of cyanide $K_2 [\text{CN}]_T$ contributes to the denominator of eq 5 and k_{obsd} has the form shown in eq 7. Rearrangement of eq 7 gives eq 8. K_2 was calculated

$$k_{\text{obsd}} = \frac{k_1 [\text{CN}]_T + K_2 k_2 [\text{CN}]_T^2}{1 + K_2 [\text{CN}]_T} \quad (7)$$

$$K_2 = \frac{k_1}{k_{\text{obsd}}} + \frac{K_2 k_2 [\text{CN}]_T}{k_{\text{obsd}}} - \frac{1}{[\text{CN}]_T} \quad (8)$$

from eq 8 using the values of k_1 and $K_2 k_2$ stated above and values of k_{obsd} from experiments in which $[\text{CN}]_T$ was greater than $2.4 \times 10^{-3} M$; $K_2 = 17 M^{-1}$. When $[\text{CN}]_T$ is less than $10^{-3} M$, $K_2 [\text{CN}]_T$ makes less than a 2% contribution to the denominator of eq 7.

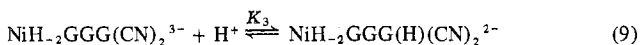
The rate of the displacement reaction is essentially independent of hydrogen ion in the pH 11-12 region; however, there is a slight increase in rate as the hydrogen ion increases from pH 11 to 9.

The intercept values of plots similar to Figure 1 are observed to decrease as a larger fraction of total cyanide is present as hydrogen cyanide. A plot of the intercept values vs. the fraction of total cyanide present as CN^- (α_{CN}) is shown in Figure 2. At high pH α_{CN} approaches 1.0 and at low pH α_{CN} approaches 0.0. The zero intercept when $\alpha_{\text{CN}} = 0.0$ indicates the absence of any hydrogen ion dependence in this pathway.

The value of K_2 decreases as the pH decreases, paralleling the conversion of cyanide ion to hydrogen cyanide. The slopes of the Figure 1 type plots increase with increasing hydrogen ion concentration.

There are at least three ways to rationalize the hydrogen ion dependence. One of these is judged to be superior to the others and will be presented in detail. The others will be briefly discussed.

The mixed complex, $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$ is believed to have two cyanides and two imide groups coordinated to nickel with the carboxylate and the amine group of triglycine not bound or weakly bound. The free amine group possesses sufficient base strength to protonate in the pH 9-11 region, eq 9. This complex then reacts with cyanide to go to prod-



ucts, eq 10. The observed rate constant for pH range 9-12

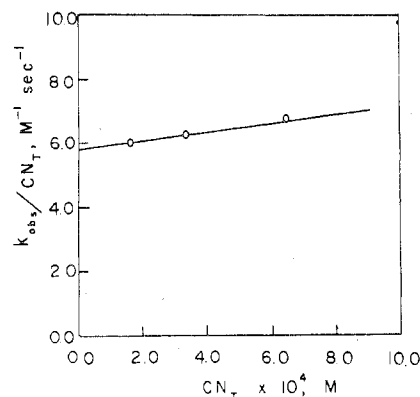
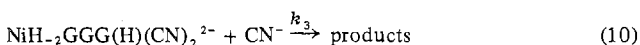


Figure 1. Resolution of the observed rate constants into components k_1 and $K_2 k_2$; $-\log [\text{H}^+] = 11$, $T = 25.0^\circ$, $\mu = 0.10 M$ (NaClO_4). See eq 6 in text.

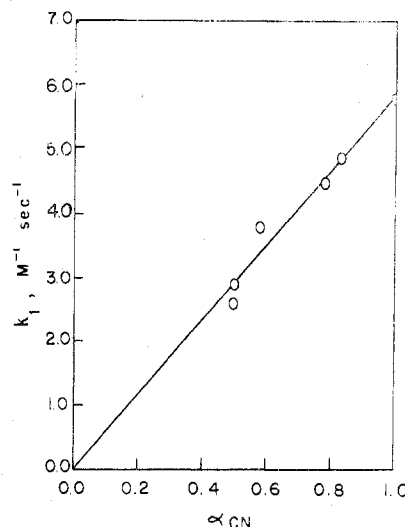


Figure 2. Dependence of k_1 on the fraction of total cyanide that is present as cyanide ion, $\alpha_{\text{CN}} = (1.0 \times 10^{-9}) / ([\text{H}^+] + 1.0 \times 10^{-9})$.

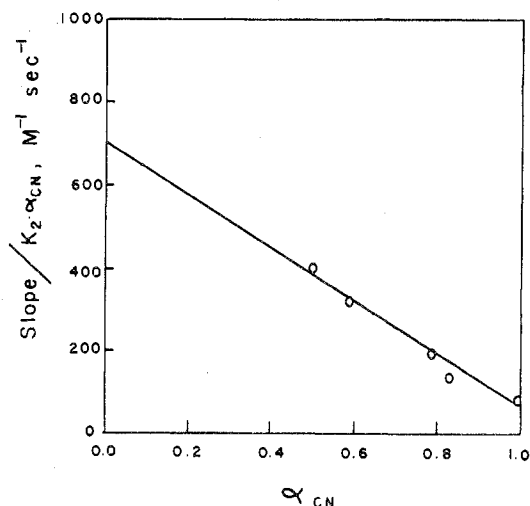


Figure 3. Evaluation of the composite rate constant $K_3 K_a k_3$ using slopes from plots of $k_{\text{obsd}}/[\text{CN}]_T$ vs. $[\text{CN}]_T$ and α_{CN} .

is shown in eq 11. Slopes of Figure 1 type plots equal $\{K_2$

$$k_{\text{obsd}} = \frac{k_1 [\text{CN}^-] + K_2 k_2 [\text{CN}^-]^2 + K_2 K_3 k_3 [\text{H}^+] [\text{CN}^-]^2}{1 + K_2 [\text{CN}^-] + K_2 K_3 [\text{H}^+] [\text{CN}^-]} \quad (11)$$

$k_2 (\alpha_{\text{CN}})^2 + K_2 K_3 k_3 \alpha_{\text{CN}} (1 - \alpha_{\text{CN}}) K_a\}$, where K_a is the acid dissociation constant for HCN and α_{CN} is the fraction of total cyanide present as CN^- . A plot of $(\text{slope}/K_2) \alpha_{\text{CN}}$ vs. α_{CN} is shown in Figure 3. The intercept for $\alpha_{\text{CN}} = 1.0$ is equal

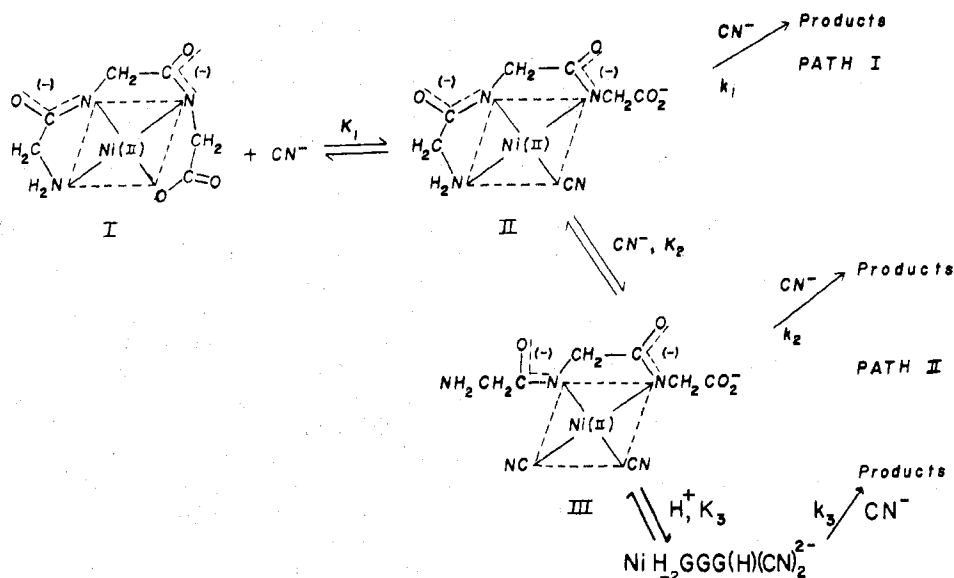


Figure 4. Schematic representation of the proposed mechanism for the reaction of nickel triglycine with cyanide.

to k_2 ; $k_2 = 70 M^{-1} \text{sec}^{-1}$. The intercept for $\alpha_{\text{CN}} = 1$ is equal to $K_3 k_3 K_a$; $K_3 k_3 K_a = 7.1 \times 10^2 M^{-1} \text{sec}^{-1}$. Equation 11 predicts hydrogen ion dependence in the pH 11-12 region if a large portion of the reaction proceeds through the $K_2 K_3 k_3$ path. In these studies the k_1 path carries most of the reaction; as a consequence the hydrogen ion dependence in the pH 11-12 region is comparable to experimental error. Table I lists the observed rate constants. It is impossible to predict k_{obsd} since $K_3 k_3$ has not been resolved.

Discussion

The reaction of cyanide with deprotonated nickel triglycine proceeds through a two-path mechanism which involves the formation of mixed complexes. The rate-determining step for each path occurs when the first nickel-imide bond breaks. A schematic description of the mechanism is presented in Figure 4. For the sake of clarity proposed structures are shown. However, it should be emphasized that the actual structures of the intermediates have not been determined.

The first step in the reaction is the rapid and complete formation of the mixed complex $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$, structure II. The cyanide ion replaces the carboxylate donor in this step. Previous studies have shown that the carboxylate group is more labile than the other donors in the copper and nickel triglycine complexes and thus the preferential replacement.^{8,9} This mixed complex can react with additional cyanide ions in two ways. The first of these, designated as path I, requires the presence of one more cyanide ion during the rate-determining step. The best description of the rate step is probably out-of-plane coordination of cyanide and breaking of the nickel-imide bond trans to the coordinated amine group. The rate constant for this step is k_1 which equals $5.9 M^{-1} \text{sec}^{-1}$. Two more cyanide ions add rapidly to complete the formation of $\text{Ni}(\text{CN})_4^{2-}$. This path carries the reaction at low cyanide concentration.

The second way that $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$ can react with additional cyanide is designated as path II. The first step in this path is the rapid but incomplete formation of a second mixed complex $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$. There are several possible configurations for this mixed complex. The one that best fits the experimental data is shown in structure III. In this complex the second cyanide is believed to replace the terminal amine group. It is possible that the second cyanide could replace an imide group; however, if this were

Table I. Rate Constants for the Reaction of Cyanide with Nickel(II) Triglycine^a

$-\log [\text{H}^+]$	$10^3 [\text{CN}]_{\text{T}}, M$	$10^3 k_{\text{obsd}}, \text{sec}^{-1}$	$-\log [\text{H}^+]$	$10^3 [\text{CN}]_{\text{T}}, M$	$10^3 k_{\text{obsd}}, \text{sec}^{-1}$
9.69	1.87	17.7	9.56	1.12	8.28
9.68	1.50	13.3	9.46	0.639	3.87
9.65	1.26	10.8	10.98	3.14	29.8
9.16	1.60	14.0	10.95	4.62	49.7
9.15	1.24	9.75	10.93	3.74	39.1
9.11	0.875	6.28	10.87	0.966	6.79
11.48	1.26	9.38	10.87	0.646	4.20
11.49	0.892	6.35	10.88	0.325	1.98
11.48	0.513	3.45	10.83	0.163	0.930
11.95	1.27	10.2	9.00	0.648	3.60
11.99	2.49	20.2	9.02	0.978	6.25
11.95	3.66	37.7	8.99	0.163	0.530
8.99	1.55	12.2	8.96	0.326	1.35
8.98	1.09	6.80	9.01 ^b	1.47	11.4
8.93	0.626	2.72	9.01 ^c	1.47	11.2
9.58	1.58	12.9			

^a At 25°, $\mu = 0.10 M$ (NaClO_4), and $[\text{Ni}]_{\text{T}} = 10^{-5} M$. ^b $[\text{Boron}]_{\text{T}} = 1.99 \times 10^{-3} M$. ^c $[\text{Boron}]_{\text{T}} = 3.98 \times 10^{-3} M$.

the case, a proton would be added in the equilibrium. This predicts that k_{obsd} would show a large decrease over the pH region of 11-12. The reaction is almost independent of pH in this region and thus it is concluded that the imide group is not being replaced. A square-pyramidal configuration is also possible; however, a transition state of this type is probably involved in path I and thus this seems unlikely. The rate-determining step in path II occurs when the third cyanide reacts. Both out-of-plane coordination sites are vacant and thus cyanide can enter at one of these positions. The rate constant for the reaction of CN^- with $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$ is k_2 which equals $70 M^{-1} \text{sec}^{-1}$.

The kinetic stabilization caused by cyanide in the mixed complex $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$ can only be realized by comparing the rates of proton transfer in the presence of EDTA⁴ and cyanide replacement. Water is capable of transferring a proton to NiH_2GGG^- with a pseudo-first-order rate constant of 0.088sec^{-1} . The resulting complex, NiH_1GGG , is rapidly scavenged by EDTA. If cyanide in $\text{NiH}_2\text{GGG}(\text{CN})^{2-}$ had no effect upon the lability of the imide group and the rate of proton transfer to this group, the slowest rate observed in this study should be that for proton transfer from water. The data in Table I show that all of the rates are less than

the 0.088 sec^{-1} value. Some are many times less. Thus cyanide imparts sizable kinetic stabilization. The exact magnitude cannot be precisely determined; however, the slowest rate in this study is $9.98 \times 10^{-4} \text{ sec}^{-1}$. This rate was free of any apparent proton-transfer contributions and thus an upper limit of $1 \times 10^{-4} \text{ sec}^{-1}$ (10% of the observed) can be set for any proton-transfer contribution. On the basis of this analysis, the stabilization would be at least a factor of 1000 and it may be more. The property of enhanced kinetic stability is also observed in the nickel-tetraglycine reactions.¹⁵ In these studies the trans imide groups cause the decrease in bond dissociation rates.

Comparison of the two rate constants k_1 and k_2 demonstrates the presence of trans labilization in low-spin nickel(II) complexes. The rate constant k_2 is 11 times k_1 ; however, both rate constants are for the breakage of a nickel-imide bond and the formation of a nickel-cyanide bond. The paths differ in the mixed complexes formed prior to the rate step. In path II cyanide is trans to the leaving group whereas in path I the terminal amine group is trans to the leaving imide group. Cyanide is a good trans-labilizing group and thus the difference in the rate constants. This difference would be greater if the electrostatic interactions were not so unfavorable. In path I the formal charges are 2- for the complex and 1- for cyanide and in path II the respective charges are 3- and 1-. This increase in substrate charge from 2- to 3- works against the trans effect.

The hydrogen ion dependence in path II is believed to be due to the protonation of the terminal amine group, structure III. From Figure 3, $K_3 k_3 K_a$ equals $7.1 \times 10^2 M^{-1} \text{ sec}^{-1}$. K_3 and k_3 have not been resolved; however, the value of k_3 should be at least as large as k_2 . With k_3 equal to $70 M^{-1} \text{ sec}^{-1}$ and $K_a = 1.0 \times 10^{-9}$, K_3 is calculated to be $1.0 \times 10^{10} M$. The protonation constant¹⁶ for glycinamide is 1.1×10^8 and for glycine 1.0×10^{10} . The electronic environment of the NH_2 group in the nickel complex is similar to that of glycine and thus a calculated value for K_3 of 10^{10} is in good agreement. If k_3 is larger than k_2 , which is pos-

sible since electrostatic repulsion is less, K_3 would be correspondingly smaller.

Another mechanism that will account for the hydrogen dependence is the direct reaction of HCN with $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$. Hydrogen cyanide reactivity is not common but several examples do exist.¹⁷⁻¹⁹ In all cases the leaving ligand has to have a basic site to accept the proton from HCN. This requirement is met; however, one wonders why there is no HCN dependence in path I and thus the first mechanism seems more feasible.

The third mechanism involves the dissociation of an imide group with concurrent protonation to form the species $\text{NiH}_1\text{GGG}(\text{CN})_2^{2-}$ which subsequently reacts with CN^- to go to products. There is no way to distinguish between this mechanism and the one presented here. The value of K_3 would probably be somewhat less; however, k_3 would be greater than k_2 and thus easily account for the difference. In general, systems react by the simplest possible mechanism and the protonation of an amine is less involved than the addition of a third path required by imide dissociation.

Cyanide is capable of displacing other aminocarboxylate ligands from nickel(II). In these complexes the nickel(II) is in the high-spin state and changes to low spin as $\text{Ni}(\text{CN})_4^{2-}$ is formed. The general mechanism for the displacement reactions requires that three cyanide ligands be bonded during the rate-determining step.^{17,20-22} There is evidence of mixed complexes prior to the rate-determining step. In the reactions of cyanide with nickel triglycine there is no change in spin state and two cyanides are present in the rate step for path I. Comparison of these systems indicates that the rate-determining step involves fewer cyanides when no change in spin state is involved.

Registry No. NiH_2GGG^- , 31011-65-1; CN^- , 57-12-5; $\text{NiH}_2\text{GGG}(\text{CN})_2^{2-}$, 51194-58-2; $\text{NiH}_2\text{GGG}(\text{CN})_2^{3-}$, 51194-59-3.

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